REMARKS

Claims 1-4, 8, 10-12, 15, 17 and 20-21 will be pending in this application after the Examiner enters the forgoing amendment.

Claim 18 is cancelled herein.

Claims 13-14 and 19 were previously withdrawn in response to a restriction requirement.

On pages 2 of the Office Action, the Examiner rejected claims 2 and 18 under 35 U.S.C. § 112, second paragraph. Applicant has amended claim 2 to address the rejection under § 112 by specifying the acronym "PVDF" as polyvinyldiene fluoride as disclosed on page 10, line 17, of the specification. Claim 18 has been cancelled consistent with the amendments to the remaining pending claims advanced herein.

The Examiner rejected claims 1-4, 8, 10-12, 15, 17, 18 and 20-21 under 35 U.S.C. § 102 as being anticipated by Asa et al U.S. Patent No. 6,214,566. Applicant has amended independent claim 1 to make more apparent differences between the claimed invention and the cited patent. Applicant respectfully submits that the pending claims are not anticipated by the Asa et al patent.

Asa et al was relied on for measuring an anti-squalene antibody using blocked squalene immobilized on a solid support which is contacted by a test sample and complexed with an indicator. Asa et al does not teach antibodies or use of antibodies that are specific in binding to squalene. Rather, as has been the subject of considerable scientific controversy, the specific teaching contained in the Asa et al patent concerns detection of squalene antibodies, based on non-specific binding, not capable of specific binding with squalene as required in the now amended claims. In

Asa et al's definitions, "Antisqualene antibody" is recited as "an antibody capable of complexing with squalene...or with any antigenic epitope presented by squalene."

While the Asa et al patent may be prophetic, the non-specific binding nature of the squalene complexes in Asa et al is further underscored by problematic disclosures. For example, Asa et el describe in Example 3 (Col. 9 lines 21-23) preparation of squalene on a solid support by "diluting" the squalene in *distilled water* at various concentrations. At the most basic level of fundamental organic chemistry, a triterpenoid hydrocarbon oil ($C_{30}H_{50}$) (extremely hydrophobic) cannot be "diluted" in water. Indeed, much of the Asa et al disclosure is essentially couched in the subjunctive mood. See, for example, Column 6: "A test sample **suspected** of containing..."; "This **may** result in the formation of a binary complex comprising squalene and antisqualene antibodies..."; "This **may** result in the formation of a terneary complex..."; This **may** be indicative of a diagnosis of Gulf War Syndrome...[c]onversely, the absence of a signal **may** indicated the absence of antisqualene antibodies..." "Squalene is a relatively large hydrocarbon which **may** contain multiple antigenic epitopes." (emphasis added). At the top of column 7, the non-specific nature of binding in the Asa et al patent is again reinforced:

> In addition, other molecules having antigenic epitopes in common with those for squalene **may** be used in an equivalent fashion. Such equivalent molecules may include...squalene precursors such as farnesyl bromide and trans-geranylacetone..."

Also, and not insignificantly, a specific antibody for squalene was not identified in the scientific literature (2000) until well after the Asa et al application was filed (1998) (See application page 3 lines 27- page 4 line 2).

Claim 1 of the present invention has been amended to positively recite that the squalene antibodies capable of specific binding with squalene is used in the detection

method and that the solid support is suitable for specific binding of squalene with squalene antibodies. On page 25 of the present application, to minimize nonspecific effects and to increase resolution and thereby overcome the problem of cross reactivity and non-specific binding, the inventors produced "monoclonal antibodies that could differentiate between SQE and SQA as antigens." Example 9 (page 26) goes on to discuss an original immunizing antigen consisting of liposomes containing SQE +LA and also specifies an "irrelevant IgM mAb" as a negative control. That is, the antigen specifically bound to squalene as the irrelevant IgM mAb did not bind to the squalene. As claim 1 has now been amended to focus on the capability of specific binding, Asa et al is not anticipatory of claim 1.

The Examiner rejected claims 5-7 and 9 under 35 U.S.C. § 103(a) as being unpatentable over Asa et al in view of either of U.S. Patent Nos. 6,191,108 to Rodkey et al and 6,166,050 to Lombardo et al. The Examiner relies on the teachings of the respective sera as blocking agents for reducing non-specific binding. Consistent with the forgoing, Asa et al does not describe, disclose, teach, or suggest specific binding to the immobilized squalene to form a specific antibody complex with little or no cross-reactivity as disclosed in the present specification at page 26 line 8. The use of the sera as blocking agents as taught in Rodkey et al and Lombardo et al with the Asa et al disclosure, does not meet the inventions now the subject of claims 5-7 and 9 which all affirmatively recite specific binding of squalene with minimal cross reactions. Accordingly, Applicants respectfully submit that there is no disclosure that would motivate modification of Asa et al by either of the Rodkey et al or Lombardo et al

patents to achieve the squalene specific binding method recited in claims 5-7 and 9 and that those claims are patentably distinct from the proposed combinations.

Dependent claim 10 recites that the ligand is a monoclonal antibody. (See Example 8). Nowhere does Asa et al describe or disclose a specific monoclonal antibody as a ligand which "exhibited strong dose dependant binding to SQE, but displayed little or no cross-reactivity to SQA". Dependent claim 16 recites that the composition comprises liposomes containing squalene. Again, squalene-containing liposomes are not mentioned or referred to in Asa et al. Claim 17 specifies that the ligand is a squalene-binding monoclonal antibody. As noted above, because the specific antibody for squalene was not reported on by Matyas et al for over a year after Asa et al was filed, not only is that patent silent about the specific squalene-binding antibody, but the Asa et al patent could not contemplate such a specific, yet-unknown entity at the time it was filed.

The Examiner rejected claim 16 under 35 U.S.C. § 103(a) as being unpatentable over Asa et al in view of U.S. Patent No. 5,709,879 to Barchfeld et al. The Barchfeld patent was relied on for teaching use of emulsion-liposome containing squalene to improve titers. Applicants respectfully traverse this finding as Barchfeld et al actually teach combining the liposomes and an antigen "prior to mixing with emulsion." (Col 22, lines30-35). Barchfeld further teaches (Col. 22, lines 36-54) that the mixed formulation of liposomes and emulsion was used for immunizing animals to increase the titers of antibodies induced against the protein antigen encapsulated within the liposomes.

Applicants submit that the present claimed invention contemplates the arrangement that is not disclosed described or contemplated by the proposed

combination. As noted above in the context of "diluting" squalene in water, squalene is a large alkene expected to behave hydrophobically. Consequently, when incorporated in into liposomes, squalene would be expected to be predominantly located in the most disordered region, deep in the liposome bilayer interior to avoid the entropically less favorable, more-ordered acyl chain region between C_2-C_{10}. Therefore, the invention of claim 16 contemplates the unexpected teaching of squalene being available for binding to specific antibodies at the surface of the liposomes rather than residing in the middle of the liposomal bilayer. In other words, the invention of claim 16 appears to present the squalene at the lipid-water interface to allow binding of specific antibodies to squalene that might be present in the aqueous region outside the liposomes. Thus, it is fair to conclude that the present claimed invention requiring that the "composition comprises liposomes containing squalene" readily distinguishes from the teachings of Barchfeld et al. alone or combination with Asa et al.

Turning to the rejection of independent claim 20, it specifically recites an assay for a squalene antibody induced by injection of squalene. Asa et al does not disclose, or suggest an assay induced by injection of squalene, which itself requires the presence of a specifically binding squalene antibody. In order to have such a method for detection of null transformed into a valid method for detection of antibodies to squalene, it would first have been necessary for antibodies capable of specific binding to squalene to be identified. In the absence of such a disclosure or teaching, it would not be possible to describe an assay method for detection of something that was not yet identified. Consequently, Applicants respectfully submit that Asa et al is not anticipatory of claim 20 or claim 21, dependant therefrom.

In view of the foregoing, Applicants respectfully solicit favorable consideration of the application as now presented and passage thereof to issue. If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned.

Respectfully submitted,

CAHN & SAMUELS, LLP

June 24, 2003

By: _____
Maurice U. Cahn, Esq.
Reg. No. 30,454
2000 P Street, N.W. (Suite 200)
Washington, D.C. 20036
Telephone: (202) 331-8777
Facsimile: (202) 331-3838